tolerance[9] and herbicide resistance[8] to a variety of other herbicides.

In conclusion, purification of a GST from susceptible black-grass revealed one polypeptide, whilst purification from a resistant black-grass biotype, which had approximately double the GST activity of susceptible biotypes, resulted in two polypeptides. The additional polypeptide had a slightly higher molecular mass and, although GST activity cannot be attributed to this polypeptide, it was eluted from a GSH affinity column with a peak of GST activity. A study of crude enzyme extracts of black-grass revealed that both atrazine and CTU can affect the enzymic conjugation of GSH with the artificial GST substrate CDNB. These observations will allow further study of herbicides' interaction with GST activity, and the role of GSTs in herbicide resistance.

ACKNOWLEDGEMENTS

We thank the Home Grown Ceareals Authority, UK for funding.

REFERENCES

1 Marrs KA, The functions and regulation of glutathione *S*-transferases in plants. *Annu Rev Plant Physiol Plant Mol Biol* **47**:127–158 (1996).

2 Anderson MP and Gronwald JW, Atrazine resistance in a velvetleaf (*Abutilon theophrasti*) biotype due to enhanced glutathione *S*-transferase activity. *Plant Physiol* **96**:104–109 (1991).

3 Moss SR and Cussans GW, Variability in the susceptibility of *Alopecurus myosuroides* (black-grass) to chlorotoluron and isoproturon. *Asps Appl Biol* **9**, *The Biology and Control of Weeds in Cereals*. pp 91–98 (1985)

4 Moss SR and Cussans GW, The development of herbicide-resistance populations of *Alopecurus myosuroides* (black-grass), in: *Herbicide Resistance in Weeds and Crops*. ed by Caseley JC, Cussans GW and Atkin RK, Butterworth-Heinemann pp 45–55 (1991)

5 Sharples CR, Hull MR and Cobb AH, The effect of herbicide safeners on chlorotoluron susceptible and resistant black-grass (*Alopecurus myosuroides*). *Proc Brighton Crop. Prot Conf – Weeds*. pp 359–360 (1995).

6 Reade JPH and Cobb AH, Purification and characterisation of a GST from the weed black-grass (*Alopecurus myosuroides* Huds.). *Pestic Sci* (submitted).

7 Cummins I, Moss S, Cole DJ and Edwards R, Glutathione transferases in herbicide-resistant and herbicide-susceptible black-grass (*Alopecurus myosuroides*). *Pestic Sci* **51**:244–250 (1997).

8 Sharples CR, Hull MR and Cobb AH, The effects of herbicide safeners on glutathione *S*-transferase activity and photosynthesis in black-grass (*Alopecurus myosuroides* Huds) susceptible and resistant to chlorotoluron. *Pestic Sci* (submitted).

9 Dixon D, Cole DJ and Edwards R, Characterisation of multiple glutathione transferases containing the GST I subunit with activities towards herbicide substrates in maize (*Zea mays*). *Pestic Sci* **50**:72–82 (1997).

Synthesis and insecticidal activity of CGA 293′343 – a novel broad-spectrum insecticide

Peter Maienfisch,* Laurenz Gsell and Alfred Rindlisbacher

Novartis Crop Protection AG, PO Box, 4002 Basel, Switzerland

Abstract: CGA 293′343 is a novel broad-spectrum insecticide currently under world-wide development by Novartis Crop Protection. CGA 293′343 belongs to a new class of highly active compounds – the neonicotinoids – and provides excellent control of a wide variety of commercially important pests. It possesses contact, stomach and systemic activity. The long-lasting residual effect is a special benefit of this compound. In general, CGA 293′343 shows biological activity in the laboratory equal to or better than the neonicotinoids so far introduced to the market. Synthetic aspects, structure–activity relationships and the biological profile are discussed.

Keywords: CGA 293′343; thiamethoxam; neonicotinoid insecticide; synthesis; [1,3,5]oxadiazinane derivatives; insecticidal activity; structure–activity relationships

1 INTRODUCTION

Neonicotinoids[1] are a novel and distinct class of insecticides. They combine selective activity against insects with a favourable safety profile, and possess contact, stomach and systemic activity, making these compounds appropriate for foliar, granular and seed treatment application. Neonicotinoids act at the nicotinic acetylcholine receptor.[2] This mode of action has so far not been broadly used for insecticides, and consequently neonicotinoids are important for controlling insects resistant to other commonly used insecticides such as organophosphates, carbamates, and pyrethroids. Imidacloprid (**1**; Fig 1)[3] was the first neonicotinoid and was introduced to the market by Bayer in 1991. As second and third neonicotinoids of the subclass chloronicotinyl compounds, nitenpyram **2**[4] from Takeda and acetamiprid **3**[5] from Nippon Soda were brought to the market in 1995 and 1996, respectively.

The extremely high activity and the unique properties of these compounds encouraged us to initiate a synthetic research project in this area. Our first attempts resulted in the synthesis of acyclic nitroenamine, cyanoamidine and nitroamidine derivatives.[6–8] Then we developed a molecular-modelling-based approach for the design of novel structural types of neonicotinoids.[9] However, the real breakthrough was achieved in 1991 with the discovery of nitroimino-[1,3,5]oxadiazinane derivatives.[10] After optimisation of this chemistry, CGA 293′343 (Fig 1) was identified as the best compound and subsequently selected for development.

CGA 293′343 (ISO draft common name: thiamethoxam) has exceptional insecticidal activity

* Correspondence to: Peter Maienfisch, Novartis Crop Protection AG, PO Box CH-4002, Basel, Switzerland.
E-mail: peter.maienfisch@cp.novartis.com
(*Received 30 June 1998; accepted 12 November 1998*)

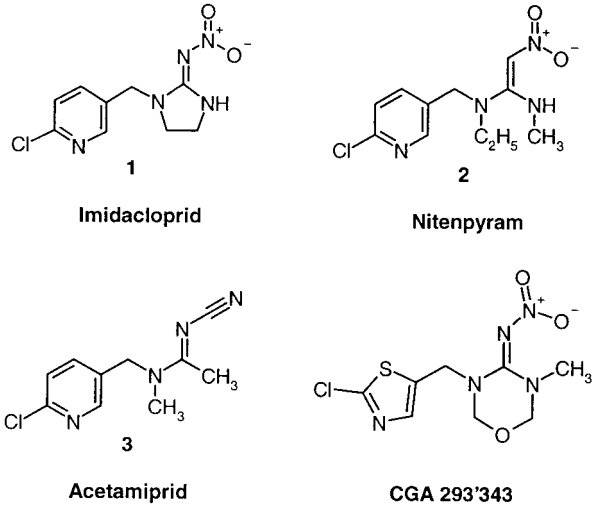

Figure 1. Chemical structures of CGA 293'343 and commercial neonicotinoids.

and was introduced into the market for seed treatment uses in 1997 in New Zealand. Possessing a 2-chloro-5-thiazolyl group as heterocyclic group, it belongs to the subclass thianicotinyl compounds and represents the first example of the second-generation neonicotinoids.

2 EXPERIMENTAL AND RESULTS

2.1 Synthesis of CGA 293'343

CGA 293'343 can be synthesized in only a few steps from easily accessible starting materials.[10] *N*-Methyl-nitroguanidine (**4**; Fig 2) is prepared according to a literature procedure[11] and then converted to the oxadiazinane **5** by treatment with formaldehyde in the presence of formic acid. Subsequent alkylation with the thiazole **6**[12] in dimethylformamide with potassium carbonate as a base afforded CGA 293'343 in good yields.

2.2 Biological laboratory evaluation of CGA 293'343

Extensive tests have been performed in our laboratory to characterise the biological activity of CGA 293'343. Table 1 shows the LC_{80} values for this compound in comparison with those of commercially available neonicotinoids. In Table 2 the activity of CGA 293'343 after seed treatment application is reported as percentage activity at a given rate in comparison to imidacloprid (**1**). After foliar application, as a drench, or into water, CGA 293'343 showed excellent activity against a wide variety of commercially important insects, such as aphids (*Aphis craccivora* Koch, *Myzus persicae* Sulz), planthoppers (*Nilaparvata lugens* Staol), whiteflies (*Bemisia tabaci* Genn), thrips (*Frankliniella occidentalis* Perg) and beetles (*Diabrotica balteata* Lec). The performance against Lepidoptera (*Spodoptera littoralis* Boisd, *Heliothis virescens* F, *Plutella xylostella*, L) is somewhat poorer. A special benefit of this compound is the outstanding residual effect observed in the laboratory against *D balteata*, *M persicae* and *N lugens* (Table 1), which clearly surpasses that of the commercial neonicotinoids imidacloprid, nitenpyram and acetamiprid.

As a seed treatment, CGA 293'343 gives very good control of all insects tested in our laboratory. The compound is also well tolerated by all crop plants used in our tests. In general, activity against *D balteata*, *M persicae* and *S littoralis* is comparable to that of imidacloprid, whereas CGA 293'343 gives clearly better results against *Aphis gossypii* Glov and *F occidentalis* (Table 2).

2.3 Structure–activity relationships

Various compounds related to CGA 293'343 were prepared following the synthetic routes described previously[10,13] and tested for contact activity (foliar

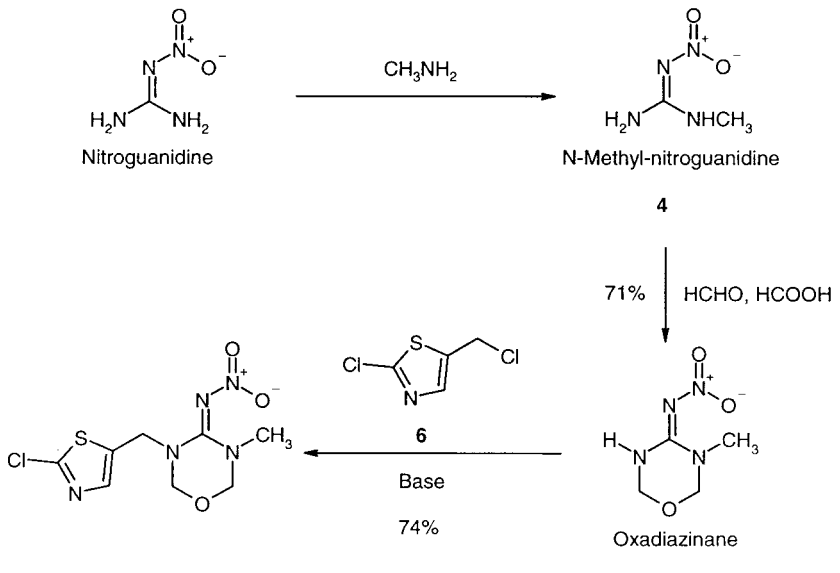

Figure 2. Synthesis of CGA 293'343.

Table 1. Spectrum of activity of CGA 293′343 and commercial neonicotinoids

Insect pest	*Stage*[a]	*Bioassay*	*LC_{80} mg AI litre^{-1}]*			
			CGA 293′343	*1*[b]	*2*[b]	*3*[b]
Spodoptera littoralis	L3	Soybean, foliar spray	100	50	>100	100
	L1	Maize, drench	12	12	nt[c]	nt
Heliothis virescens	L1	Soybean, foliar spray	12	12	>100	3
Plutella xylostella	L3	Soybean foliar spray	100	100	>100	25
Diabrotica balteata	L3	Sandy soil, foliar spray	0.2	0.8	>100	12
	L3	Sandy soil, foliar spray, persistence 30 days[d]	0.8	3	nt	12
	Adult	Bean, foliar spray	12	12	nt	25
	Adult	Bean, drench	0.05	0.8	nt	nt
Aphis craccivora	mp	Pea, foliar spray	3	3	3	3
	mp	Pea, into water	12	12	12	12
Myzus persicae	mp	Pepper, foliar spray	0.8	0.8	3	3
	mp	Pepper, drench, persistence 28 days[d]	0.8	0.8	3	>12
Bemisia tabaci	N2	Bean, foliar spray	3	3	12	25
Nilaparvata lugens	N2	Rice, foliar spray	0.8	0.8	0.8	100
	N2	Rice, foliar spray, persistence 4 days[d]	3	25	12	>100
	N2	Rice, into water, persistence 21 days[d]	0.05	0.2	0.2	3
Frankliniella occidentalis	mp	Bean, drench	3	12	nt	nt

[a] L1, L3: 1st, 3rd instar larvae; N2: 2nd instar nymph; mp: mixed population.
[b] 1 = imidacloprid; 2 = nitenpyram; 3 = acetamiprid.
[c] nt = not tested.
[d] Days after treatment when infestation with insects was made.

spray) against *A craccivora* as a model system for structure–activity analysis. In this test, pea seedlings infested with a mixed population of *A craccivora* are treated with the test solution and the samples are checked for mortality six days after introduction of the insects. The LC_{80} value for CGA 293′343, was 3 mg litre^{-1}.

The structure–activity relationships for the pharmacophore N-C(N) = X, the oxadiazinane ring, the substituent R and the heterocyclic group Het were elucidated. A summary of the results is outlined in Fig. 3.

We first focused our attention on the influence of the pharmacophore N-C(N) = X. Among the compounds tested, best activity was observed for the nitroamidine pharmacophore (N-C(N) = N-NO_2). Replacement of the nitroimino group by a cyanoimino group clearly diminished the activity, while

Table 2. Activity of CGA 293′343 after seed treatment application

Insect pest	*Stage*[a]	*Bioassay (days)*[b]	*Rate (mg AI per seed)*	*Mortality (%)*	
				CGA 293′343	*Imidacloprid*
Spodoptera littoralis	L1	Corn (11)[b]	0.03	17	28
		Corn (32)	0.03	77	63
Diabrotica balteata	Adult	Corn (11)	0.03	100	100
		Corn (47)	0.03	95	95
Diabrotica balteata	L3	Corn (14)	0.03	100	100
		Corn (29)	0.03	97	100
Aphis gossypii	mp	Cotton (14)	0.03	100	78
		Cotton (48)	0.03	77	20
Myzus persicae	mp	Cabbage (14)	0.03	100	100
		Cabbage (48)	0.03	100	100
Frankliniella occidentalis	mp	Cotton (14)	0.3	100	89
		Cotton (41)	0.3	70	13

[a] L1, L3: 1st, 3rd instar larvae; mp: mixed population.
[b] Days after sowing when infestation with insects was made.

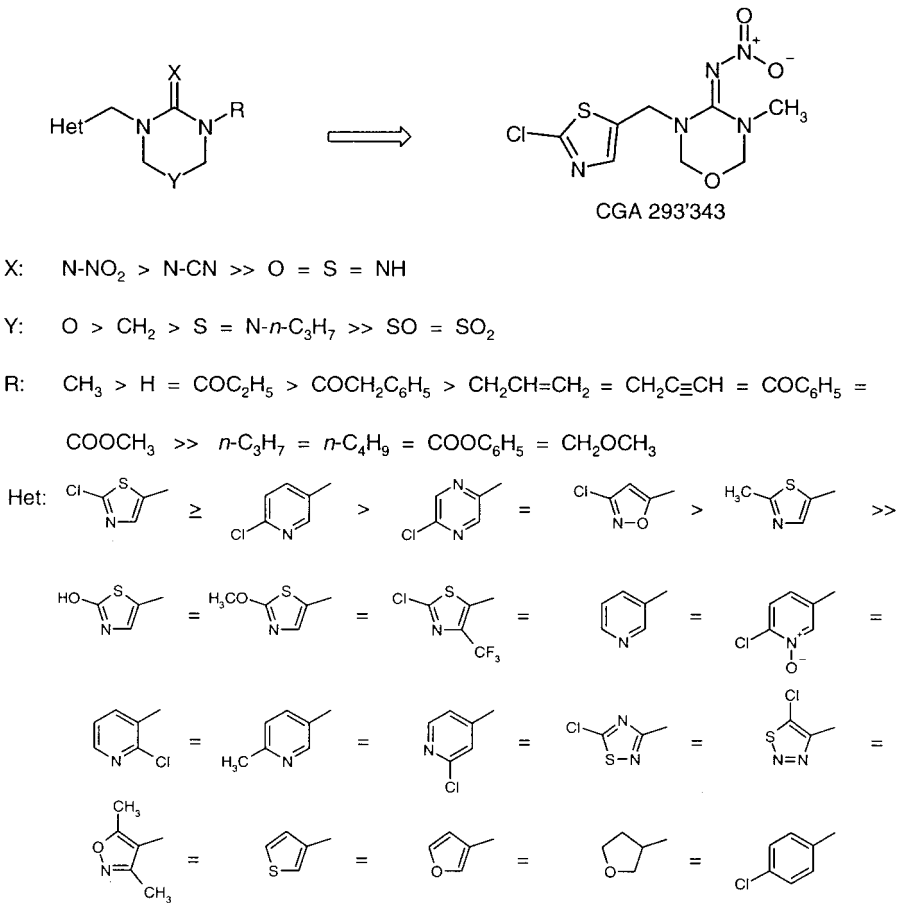

Figure 3. Structure–activity relationships for nitroimino-[1,3,5]oxadiazinane derivatives.

compounds with X = O, S or NH were not effective at 100 mg litre^{-1}.

Variations of the [1,3,5]oxadiazinane ring revealed a strong dependence of the efficacy on the nature of Y. Replacing O by a CH_2-, S- or *N*-alkyl group resulted in a decrease of the activity. Interestingly, if the sulfur in the [1,3,5]thiadiazinane ring (Y = S) is further oxidised to the corresponding sulfoxide and sulfone respectively, a drastic loss of activity is observed.

The effect of the substituent R on the nitrogen was studied extensively. Compounds where R is hydrogen possess excellent activity. A lower level of potency is observed with an acyl, allyl or propargyl group, while a *n*-propyl, *n*-butyl or methoxymethyl group led to almost total loss of activity. Surprisingly, introduction of a methyl group resulted in a clear increase in biological activity.

The structure–activity relationships for the heterocyclic group (Het) were also investigated. 2-Chloro-5-thiazolyl derivatives gave the best activity and the 2-chloro-5-pyridyl compounds were equally or somewhat less active. Replacement of the chloro substituents by hydrogen, methyl, hydroxy or methoxy caused a drastic loss of activity. Adding a trifluoromethyl group at the 4-position of the thizaole heterocycle led to a clear decrease in activity. Changing the 2-chloro-5-pyridyl into a 2-chloro-1-oxy-5-pyridyl, a 2-chloro-3-pyridyl or a 2-chloro-4-pyridyl resulted in a drastic loss of activity. These data show that efficacy is strongly influenced by the nature of the substituents and their position on the pyridyl or thiazolyl ring. Compounds with other heterocyclic groups such as 5-chloro-[1,2,4]thiadiazol-3-yl, 5-chloro-[1,2,3]thiadiazol-4-yl, 3,5-dimethyl-4-isoxazolyl, 3-furanyl, 3-thiophenyl and tetrahydro-3-furanyl or a 4-chlorophenyl group were not effective at 100 mg litre^{-1}. Replacement of the 2-chloro-5-thiazolyl or the 2-chloro-5-pyridyl group by a 5-chloro-2-pyrazinyl or a 3-chloro-5-isoxazolyl group also led to compounds showing good activity.

The structure–activity relationships can thus be summarised as follows: as pharmacophore the nitroamidine N-C(N) = N-NO_2 is best. The [1,3,5]oxadiazinane ring is clearly superior to the tetrahydropyrimidine, the [1,3,5]triazinane and the [1,3,5]thiadiazinane ring. 2-Chloro-5-thiazolyl is the most promising heterocyclic system and a methyl group as substituent R on the nitrogen is more favourable than a hydrogen.

3 CONCLUSIONS

CGA 293'343 (ISO draft common name: thiamethoxam) is a new neonicotinoid insecticide currently under world-wide development by Novartis Crop Protection. Belonging to the subclass thianicotinyl compounds, it represents the first

example of the second-generation neonicotinoids. CGA 293′343 provides excellent control of sucking and chewing insects. Control of most insect pests with CGA 293′343 is superior or equivalent to that of currently registered neonicotinoid insecticides. Structure–activity relationships revealed that variation of the pharmacophore, the oxadiazinane ring, the heterocylcic group and the substituent R in CGA 293′343 diminish biological activity against *Aphis craccivora*.

REFERENCES

1 Yamamoto I, Neonicotinoids – mode of action and selectivity. *Agrochem. Jpn* **68**:14–15 (1996).
2 Tomizawa M and Yamamoto I, Binding of nicotinoids and related compounds to the insect nicotinic acetylcholine receptor. *Nihon Noyaku Gakkaishi* (*J Pestic Sci*) **17**:231–236 (1992).
3 Elbert A, Overbeck H, Iwaya K and Tsuboi S, Imidacloprid, a novel systemic nitromethylene analogue insecticide for crop protection. *Proc Brighton Crop Prot Conf – Pests and Diseases*. Vol 1, pp 21–28 (1990).
4 Minamida I, Iwanaga K, Tabuchi T *et al*, Synthesis and insecticidal activity of acyclic nitroethene compounds containing a heteroarylethylamino group. *Nihon Noyaku Gakkaishi* (*J Pestic Sci*) **18**:41–48 (1993).
5 Takahashi H, Mitsui J, Takakusa N *et al*, NI-25, a new type of systemic and broad-spectrum insecticide. *Proc Brighton Crop Prot Conf – Pests and Diseases*. vol 1, pp 89–96 (1992).
6 Gsell L, Preparation and testing of [(pyridylmethyl)-amino]nitroethylenes as insecticides, acaricides, and ectoparasiticides. *Eur Pat Appl EP 302833 A2 890208* (1987)
7 Gsell L, Preparation of pyridylmethylcyanoguanidines as insecticides and acaricides. *Eur Pat Appl EP 306696 A1 890315* (1987).
8 Kristiansen O, Maienfisch P and Gsell L, Guanidine derivatives as insecticides. *Eur Par Appl EP 418199 A2 910320* (1989)
9 Maienfisch P, Gonda J, Jacob O *et al*, Synthesis and insecticidal activity of novel nicotinoids. *Book of Abstracts, 214th ACS National Meeting, Las Vegas, NV*, 7–11 *September AGRO-018*. American Chemical Society, Washington, DC (1997).
10 Maienfisch P and Gsell L, Preparation of 3-(heterocyclylmethyl)-4-iminoperhydro-1,3,5-oxadiazine derivatives as pesticides. *Eur Pat Appl EP 580553 A2 940126* (1992).
11 McKay AF and Wright GF, Preparation and properties of *N*-methyl-*N*-nitroso-*N*′-nitroguanidine. *J Am Chem Soc* **69**:3028–3030 (1947).
12 Uneme H, Higuchi N and Minamida I, Preparation of chlorothiazole derivatives. *Eur. Pat. Appl., EP 446913 A1 910918* (1990).
13 Maienfish P and Gsell L, Preparation of substituted 4-nitroiminoperhydro-1,3,5-oxadiazine derivatives and their use as pesticides. PCT Int Appl, *WO 9806710 A1 980219* (1996).

Synthetic approaches towards CGA 293'343: A novel broad-spectrum insecticide

Thomas Göbel,[1] Laurenz Gsell,[2] Ottmar F Hüter,[2] Peter Maienfisch,[2] Rudolf Naef,[3] Anthony C O'Sullivan,[2] Thomas Pitterna,[2]* Thomas Rapold,[4] Gottfried Seifert,[4] Marcel Senn,[5] Henry Szczepanski[2] and David J Wadsworth[1]

[1] *Novartis Animal Health Inc, PO Box, CH-4002 Basel, Switzerland*
[2] *Novartis Crop Protection AG, PO Box, CH-4002 Basel, Switzerland*
[3] *Novartis Services AG, PO Box, CH-4002 Basel, Switzerland*
[4] *Novartis Crop Protection Münchwilen AG PO Box, CH-4333 Münchwilen, Switzerland*
[5] *Novartis Crop Protection Monthey SA, Route de l'Ile au Bois CH-1870 Monthey, Switzerland*

Abstract: Synthetic approaches towards CGA 293'343 (ISO draft common name: thiamethoxam), a novel broad-spectrum insecticide from the class neonicotinoids, are described. 2-Chloro-5-chloromethylthiazole, an important synthetic intermediate, was prepared from five different precursors. Alternatively, CGA 293'343 was prepared via the intermediate 2-benzylmercapto-5-chloromethylthiazole, the synthesis of which is also described.

Keywords: CGA 293'343; thiamethoxam; neonicotinoid; insecticide; thiazole; oxadiazinane; synthesis

1 INTRODUCTION

CGA 293'343[1] (Fig 1; ISO draft common name: thiamethoxam), which is a novel broad-spectrum insecticide, shows outstanding activity against a wide spectrum of important pests; it belongs to the class of neonicotinoids[2] and is currently under worldwide development by Novartis Crop Protection. In the course of development, the need for a practical and economically viable synthesis arose.

One synthesis of CGA 293'343 utilises the route shown in Fig 1. Reaction of 2-chloro-5-chloromethylthiazole **2** with the oxadiazinane intermediate **1** gave the desired product in good yield. Therefore, the core task to be addressed in the synthesis plan was the construction of the chlorothiazole moiety.

To date, apart from our work, five synthetic routes for compound **2** have been published. When we started out on our endeavour, only two references[3,4] were known. Neither route satisfied our need for a high-yielding, economically and ecologically sound process. After completion of our synthetic studies, further synthetic routes[6–8] were subsequently

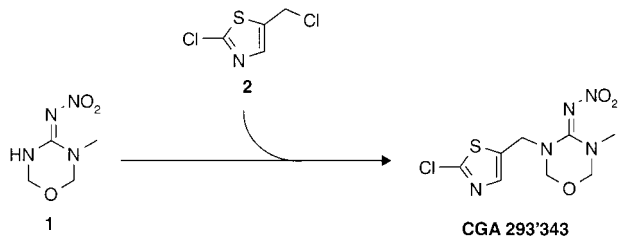

Figure 1. Synthesis of CGA 293'343 from the intermediate **2**. Reaction conditions: DMF, K_2CO_3, 2 h, 60°C, 74%.

*Correspondence to: Thomas Pitterna, Novartis Crop Protection AG, PO Box, CH-4002 Basel, Switzerland.
E-mail: thomas.pitterna@cp.novartis.com

(*Received 30 June 1998; accepted 12 November 1998*)